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BRIEFING PAPER

SCIENTIFIC STANDARD-SETTING ORGANIZATIONS
IN ASIA AND LATIN AMERICA

Introduction

One of the problems that faced the industry in connection with the U.S. Environmental Protection Agency's recent report on environmental tobacco smoke was the ambiguity of the applicable guidelines for carcinogenic risk assessment. In classifying ETS as a "Group A" carcinogen, the EPA resolved all ambiguities against ETS. In addition, EPA ignored the guidelines entirely insofar as they appeared to require a classification other than the classification the pertinent EPA officials desired.

When challenged on the latter point, EPA officials simply claimed that the agency's guidelines for carcinogenic risk assessment were never intended to be applied in a rigid or dogmatic manner. They also sought to take refuge in the notion that a Group A classification of ETS was justified by the "weight of the evidence," an assertion that was designed effectively to prevent challenges to EPA's classification decision on ETS.

Full risk assessments are much less often undertaken in Asia and Latin America than in the U.S. Instead, governments (and individual scientists) in those regions tend to rely upon pronouncements made by groups such as the International Agency for Research on Cancer and by recognized "authorities" such as the U.S. EPA.

A fair review of the available data would conclude that ETS has not been shown to cause or increase the risk of lung cancer among nonsmokers. This briefing note describes an initiative that might be launched in Asia and/or Latin America in support of efforts to (1) discourage governments in those regions from simply adopting the U.S. EPA's carcinogenicity finding on ETS and (2) prevent a similar conclusion being reached because of the application of risk assessment "guidelines" as ambiguous and flexible as those employed by the U.S. EPA.

Classification Standards for Carcinogenic Risk Assessment

Both the U.S. EPA and IARC have developed, and at least IARC purports to apply, guidelines for carcinogenic risk assessment. For the U.S. EPA, the guidelines state that substances should not be classified within "Group A" -- a category that is reserved for "known human carcinogens" -- unless there is --

* "sufficient" epidemiologic data consistently reporting an association between the particular exposure and disease, and

* a determination that neither confounding factors nor bias could be responsible for the association.

The U.S. EPA's carcinogenicity guidelines do not define with any precision what, apart from consistency, is needed before epidemiologic data can be deemed to be "sufficient." The most frequently cited criteria for assessing whether an observed association might be sufficient to establish or strongly suggest a causal relationship are the criteria that were described by Sir Austin Bradford Hill in 1965. Those criteria include:

* strength and consistency of the association

* absence of bias

* appropriate temporal sequence

* demonstrable dose-response relationship

* specificity

* biological plausibility

* experimental evidence

While both the U.S. EPA and IARC have elaborated upon the Bradford Hill criteria to some extent, the elaborations still leave many questions unanswered. For example, so far as strength of association is concerned, neither entity has provided any guidance on what constitutes a "weak" as opposed to "strong" association (i.e., is any relative risk below 3.0 a "weak" association). One possible explanation for the failure of the U.S. EPA and IARC to address that question may be that the Bradford Hill criteria attempt to cover epidemiologic data collected in many different types of study. The fact remains, though, that the failure to define "weak" and "strong" associations leaves a very substantial ambiguity,

which the U.S. EPA moved to exploit in its recent report on ETS.

A further example of the ambiguity that pervades the current EPA/IARC guidelines on carcinogenicity appears in IARC's Cancer: Causes, Occurrences and Control (IARC Scientific Publications, No. 100, Lyon, France 1990). After having noted there that an appropriate temporal sequence between exposure to a substance and the appearance of cancer is essential to any finding of carcinogencity but is not alone determinative, IARC went out of its way to avoid setting a threshold for the required strength of association. Instead, IARC seemed content to create a kind of sliding scale, observing that "[s]till different degrees can be perceived in the strength of * * * [the] suggestion" of carcinogencity.

In sum, the carcinogencity guidelines applied by the U.S. EPA and IARC leave substantial unanswered questions and have substantial gaps. Convincing pertinent bodies in Asia and Latin America to remove some of the ambiguity from the U.S. EPA/IARC carcinogencity guidelines so far as low-risk environmental epidemiology is concerned could pay substantial dividends -- both in creating a standing rationale that could be used to oppose automatic adoption in Asia and Latin America of the U.S. EPA's classification of ETS and in preparing for full-scale consideration of ETS in countries in those regions.

Specifically, future consideration of ETS and carcinogencity would be facilitated if pertinent bodies in Asia and Latin America were to issue pronouncements along the following lines:

(1) Relative risks of 2.0 or less should be regarded as "weak" and should be interpreted with caution, requiring among other things special attention to be paid to possible bias and confounding;

(2) Statistical significance should be assessed by a two-tailed test looking toward a 95 percent confidence interval;

(3) "Sufficient" evidence of carcinogicity should never be found whenever the majority of the available studies do not reach statistical significance as defined in Item 2 above;

(4) A meta-analysis should not be undertaken unless the pertinent studies are similar in design, focus on similar or comparable populations, utilize consistent definitions and address the issues of bias and confounding in a manner permitting those issues to be taken into account in interpreting the results of the meta-analysis;

(5) A risk assessment for a particular substance should never be based, in whole or in part, upon epidemiologic data relating to another substance unless it can be shown that any differences in the two substances are insignificant from both a chemical and physical standpoint; and

(6) A positive carcinogencity finding should not be made based on high dose exposures for a substance encountered only at low doses unless it can be shown that the same biological mechanisms apply at both high and low doses.

Prompting the Desired Pronouncements

One approach to prompting pronouncements along the lines described above would be to "seed" the holding of workshops in various countries in Asia and Latin America to which leading scientists might be invited. Organizations (e.g., government bodies, professional/academic societies, etc.) concerned about environmental issues might be approached to sponsor the workshops. National statistical associations also might be prevailed upon to tackle issues of special concern to their members (e.g., the use of two-tailed tests and 95 percent confidence intervals). With respect to the latter, it might even be possible to convince selected scientific journals in Asia and Latin America to include in their instructions to authors that 95 percent confidence intervals should be used in reporting relative risks.

(i) Specific Opportunities in Asia

Professional/academic societies qualified to address the issues described above already exist in some of the more scientifically sophisticated countries in Asia. That is particularly true of Japan and Korea.

There are many learned societies in Japan that might address the issue of carcinogenic risk assessment. Two promising candidates would be the societies that cosponsored the 1993 Tokyo ETS symposium -- the Society of Environmental Sciences, Japan, and the Japan Indoor Air Research Society. Either or both organizations might be encouraged to address the issues discussed above, perhaps in conjunction with other pertinent organizations such as the Japan Epidemiologic Association.*/

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*/ A word of caution is probably appropriate so far as the Japan Epidemiologic Association or any other national or international professional organization dominated by

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In Korea, the National Institute of Health, National Institute of Safety Research and the Korean Center for Toxic Chemicals are all nationally recognized bodies that might be willing to make pronouncements on the treatment of epidemiologic data. The Korean Society of Statistics, Korean Society of Biostatistics and the Korean Association of Epidemiology also might be approached. We know several Korean scientists who might lead the effort in Korea, although substantial additional thought and "spadework" would have to be completed before we would be confident in offering firm recommendations.

The scientific community in Hong Kong and Singapore are small and are dominated by the scientists affiliated with the local or national universities. An initiative along the lines described above in Hong Kong and Singapore undoubtedly would have to be university based. In both places, we have contacts that would permit us to explore undertaking such an initiative. Because of the hostility toward tobacco that exists in both places, avoiding any appearance that the effort was geared at "protecting" the interests of the tobacco industry would be especially important.

There are few learned societies in Malaysia, Indonesia, Thailand or the Philippines. In those countries, relying upon leading scientists affiliated with local or national universities might be possible. Alternatively, we might be able to prevail upon our consultants in those countries to organize stand-alone meetings, to which a number of selected non-consulting scientists (including government scientists) might be invited. Alternatively, we might consider involving a regional organization such as the Asian Association for Occupational Health, within which we have excellent contacts.

Making real progress in China probably would require the involvement of scientists working for the government. We do have contacts with university-affiliated scientists in China who may be able to make appropriate arrangements.

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epidemiologists is concerned. Epidemiologists (perhaps no more or less than any other professional group) can be expected to view with some hostility efforts aimed at limiting the perceived significance of the work that they do. As a consequence, we would not think it prudent to entrust the issues described in this briefing note to a group composed or dominated by epidemiologists without careful checks on the inclinations of the group and/or making sure that the group actually opining on the issues of concern to us was carefully balanced.

Again, further investigation would be prudent before we would feel comfortable offering firm recommendations.

Finally, Taiwan presents something of a dilemma so far as the initiative described above is concerned. We have few scientific contacts in Taiwan and no actual consultants, a circumstance that we are attempting -- albeit thus far without success -- to remedy. The major roadblock for us in Taiwan has been that scientists who work for the government, which includes university-affiliated scientists, are not permitted to enter into consulting relationships. The Taiwan Government maintains, as a consequence, virtually complete control over the scientific work that is done -- indeed, even controls what is submitted for publication. If the initiative described above is undertaken in Asia, we would not recommend beginning with Taiwan.

(ii) Specific Opportunities in Latin America

As in Asia, some countries in Latin America are far more sophisticated scientifically than others. Chile, Argentina, Brazil, Costa Rica and Venezuela are perhaps the most advanced. They are consequently also the Latin countries in which the initiative described above would be most valuable if completed successfully.

There are National Academies of Science in several Latin countries. A good example is the Argentine National Academy of Science, whose president chaired an indoor air quality symposium in the late 1980s and continues to be both cordial and cooperative.

There are also other opportunities in Argentina. Government and public opinion in Argentina have been shaped or affected in the past on some issues by the work of ad hoc scientific groups, relying upon private funding while involving eminient local and international scientists. One of the scientists with whom we currently are working in Argentina has suggested that we consider putting together such a group to address the issues described above (perhaps denominating the group the "Argentine Council on Risk Assessment Issues").

There are no organizations in Chile focusing on risk assessment issues, although -- as in Argentina -- a Chilean National Academy of Sciences does exist. We believe there is some prospect of our approaching the Chilean National Academy of Sciences on epidemiologic/risk assessment issues, using the good offices of our current consultants in Chile. Alternatively, and again as in Argentina, it may be possible in Chile to create an ad hoc group of scientists to address the issues described above.

Many scientific societies exist in Brazil that might be approached to look at epidemiolgic/risk assessment issues.

Our scientific contacts in Brazil are sufficiently good that we would be reasonably confident of our ability to interest one or more of the existing scientific societies in Brazil to address the issues that concerns us.

There is a relatively new National Academy of Sciences in Costa Rica. While that may facilitate our gaining access to the group's agenda, it also means that the group's pronouncements may not be given much weight -- or at least not as much weight as they would be given if the group had established more of a track record than it have been able thus far to establish. The Caja Costarricense de Seguro Social, the national body responsible for public health issues in Costa Rica, typically refers to U.S. EPA and/or IARC guidelines in reaching conclusions on carcinogenicity issues.

It is possible, but by no means certain, that the Caja Costarricense de Seguro Social could be prevailed upon to consider proposed refinements to the EPA/IARC carcinogenicity guidelines. Again, further investigation would be required. We also might investigate further the possible involvement of the Instituto Costarricense de Investigacion y Ensenanze en Nutricion y Salud, a prestigious Costa Rican research institute that focuses primarly upon nutrition and health issues.

There are several environmental agencies in Venezuela, the most important of which is FUNDENA. Since one of the scientists with whom we have been working in Venezuela has close contacts with several members of FUNDENA's board of directors, there may be a substantial chance of our being able to interest FUNDENA in the issues described above.

For other countries in Central and South America, consulting scientists may be able to organize stand-alone meetings or prompt university-based consideration of the issues that are of concern to us. Expertise on epidemiologic and risk assessment issues tends to be sparse in such countries, however, so that the participation of foreign scientists would be essential.

Timing and Cost Considerations

Since we have scientific consultants in most Asian and Latin American countries, we should be able to move reasonably promptly in most countries to complete the investigation of potential forums for consideration of the issues described above and actually schedule consideration of such issues. In fact, in some countries six to nine months may be all that would be required to complete the meetings and other work that would be required and issue a report. Formal publication of the report, or of a summary of the report, in a scientific journal may take a further three to six months.

So far as cost is concerned, we generally envisage small workshops rather than large symposia. The workshops could be closed to anyone not specifically invited or be open to all society members. The largest category of costs that we would incur would be the compensation that we would have to pay our local consultants as well as any consultants who might be needed from outside the target country. Finally, we personally would incur time and expenses in organizing and guiding the effort, the magnitude of which would vary from country to country. For a "typical" country, and barring unforeseen difficulties, between $30,000 and $50,000 probably would have to be budgeted to complete the initiative.

The Logical Next Step

In view of the novelty of the initiative described above, we would recommend that the effort described in this briefing paper first be "test marketed" in a couple of key countries. That would permit us to complete the investigations that would be required and develop a detailed budget for the target country or countries. Japan, Argentina and Brazil would our leading "test market" candidates.

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